FORM 2

THE PATENTS ACT, 1970
(39 OF 1970)

COMPLETE SPECIFICATION
(See section 10)

PROCESS FOR THE PREPARATION OF CRUDE 1-[3-(DIMETHYLAMINO) PROPYL]-1-(4-FLUOROPHENYL)-1,3-DIHYDRO-5-ISOBENZOFURAN CARBONITRILE BASE

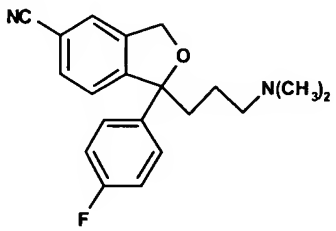
SUN PHARMACEUTICAL INDUSTRIES LTD.

A company incorporated under the laws of India having their office at ACME PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059. MAHARASHTRA, INDIA

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed.

PROCESS FOR THE PREPARATION OF CRUDE 1-[3-(DIMETHYLAMINO) PROPYL]-1-(4-FLUOROPHENYL)-1,3-DIHYDRO-5-ISOBENZOFURAN CARBONITRILE BASE

This invention provides a process for the preparation of crude 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base with substantilly low levels of impurities. 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile, commonly known as citalopram (INN Name) is a compound of **Formula I**. 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base with substantially low levels of impurities is useful in obtaining salts of 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile, in particular, 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile hydrobromide of pharmaceutical quality by a simple process. 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile hydrobromide is a well known antidepressant.

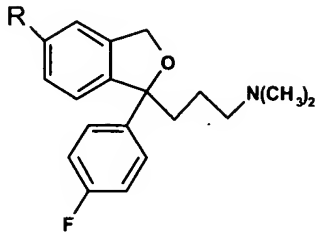


Formula I

PRIOR ART:

United States Patent No.4,136,193 (Indian reference not available, hereinafter referred to as '193) claims 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile or its pharmaceutically acceptable acid addition salt. It

discloses a process for the preparation of 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile from the penultimate 5- substituted derivatives, compounds of **Formula II** wherein R is halogen or trifluoromethyl, by reaction with cyanide source.



Formula II

The exchange process described for the preparation of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile gives the desmethylcitalopram and other high molecular weight impurities in unacceptable amounts. Purifying such an impure material makes the process economically unviable.

United Kingdom patent No. GB 2356199 (Indian reference not available) included examples wherein 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile crude base was prepared by the cyanide exchange process but with sufolane as a solvent, instead of dimethylformamide as reported in **'193.** It is disclosed in the patent that the cyanide exchange process of '193 patent results in formation of high molecular weight impurities including dimeric reaction products in unacceptable amounts. The use of film distillation process was made to obtain higher purity 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base. The patent claims this process with additional purification steps that are required.

PCT publication WO 0011926 discloses the conversion of compound of **Formula II** wherein R maybe Cl or Br to 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile or its pharmaceutically acceptable salt with a cyanide source

in the presence of a nickel catalyst. The process was stated to result in 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile in high yield as a very pure product.

PCT publication WO 0013648 discloses the conversion of compound of **Formula II** wherein R maybe bromo or iodo to 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile or its pharmaceutically acceptable salt with a cyanide source in the presence of a palladium catalyst which is expensive.

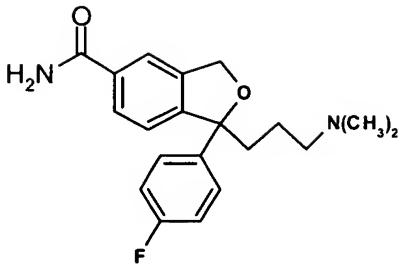
PCT publication WO 0102383 discloses the synthesis of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile by reaction of compound of **Formula II** wherein R is a halogen atom, preferably bromine with activated magnesium to form the Grignard reagent followed by reaction of the Grignard with a compound containing a –CN group bound to a leaving group. The reported process enables 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile in high yields.

PCT publication WO 0145483 discloses the cyanide exchange reaction of compound of **Formula II** wherein R maybe iodo, bromo, chloro or CF_3-$(CF_2)_n$-SO_2-O-, n-being 0,1,2,3,4,5,6,7, or 8 to give 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile or its pharmaceutically acceptable salt with a cyanide source. The crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base has a purity of about 85% which is optionally subjected to some initial purification and treatment with an amide or an amide-like forming agent, acid/base wash and/or crystallization and recrystallization of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile in order to remove the amides formed and the resulting 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile product is optionally further purified, worked up and isolated as the base or pharmaceutically acceptable salt thereof. This process involves a laborious work-up procedure to obtain high purity 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile.

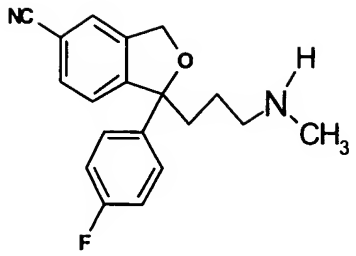
Several other patents report the preparation of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile with different starting materials viz.

1. Conversion of 5-amido or ester group to a 5-cyano group (WO 9819513)
2. Conversion of 5-amino group to a 5-cyano group (WO 9819512)
3. Conversion of 5- formyl group to a 5-cyano group (WO9930548)
4. Conversion of 5-oxazolinyl or thiazolinyl group to 5-cyano group (WO 0023431)
5. Conversion of 5-substituted groups like R_1R_2N-CO- or 4,5-dihydro-1,3-oxazol-2--yl optionally substituted in the 4- and or 5-position with one or more alkyl, aryl or heteroaryl groups to the 5-cyano group (WO 9930548)

The major impurities that are formed when the cyanide exchange process as disclosed in '193 patent is followed are 5-carboxamide –1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-phthalide, a compound of **Formula III,** and desmethylcitalopram, a compound of **Formula IV,** along with unconverted starting material. The process described in the **'193** patent involves refluxing the reaction mixture in DMF for 4 hours followed by isolation of product to get the crude base. However, under these conditions we observed the presence of 10-25% of starting material along with amide and descitalopram as impurities and found it extremely difficult to purify the product to the desired levels. Even when the reaction was continued for several hours (>15 hours) the unreacted starting material remained in the range of 0.5 to 5 % and purity of the desired product decreased to about 60%. It was observed that high molecular weight impurities were formed. The formation of these impurities increased with increase in duration of reaction time to values as high as 20%. These impurities were difficult to remove by usual work up procedure leading to extensive and expensive purification process.



Formula III



Formula IV

OBJECTIVES OF THE INVENTION

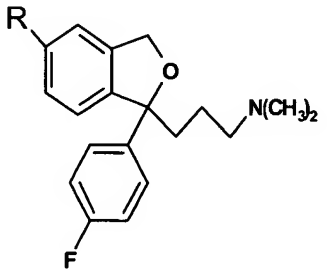
The objective of the present invention is to provide crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base with substantially low levels of impurities and thus avoid an extensive and expensive purification process.

It is a further objective of the present invention to arrest the formation of substantial amount of carboxamide impurity, high molecular weight impurities and to suppress desmethylcitalopram besides taking the cyanide exchange reaction to nearing completion so as to obtain crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base in substantially high purity.

A simple process for the preparation of crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base with low level of impurities has been found. The process avoids the extensive work-up of the prior art processes.

SUMMARY OF THE INVENTION

The present invention provides a process for the preparation of crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base with substantially low levels of impurities, the process comprising reacting a compound of the **Formula II**



Formula II

wherein R is Cl or Br with a cyanide source in presence of an iodide and a non polar aprotic solvent.

The process of the present invention provides crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base with substantially low levels of impurities.

According to the process of the present invention the cyanide source may be selected from KCN, NaCN, CuCN, $[(R')_4N]$ CN where $(R')_4$ indicates four groups which may be the same or different selected from hydrogen and straight chain or branched alkyl, and the like, preferably KCN, NaCN and CuCN, the most preferred being CuCN.

According to the process of the present invention the iodides that may be used in the present invention are selected from stable metal iodides, alkali and alkaline earth metal iodides.

According to the process of the present invention the preferred iodides being alkali and alkaline earth metal iodides and the most preferred being alkali metal iodides like potassium iodide.

According to the process of the present invention the preferred iodide is employed is in the mole ratio of 0.1-10 moles preferably 1-5 moles, the most preferred being 1-3 moles.

According to the process of the present invention the non polar aprotic solvent may be selected from the group of amides, amines and polyethers.

According to the process of the present invention the amide solvents may be selected from N,N-dialkyl, N-alkyl,N'-aryl, N,N-Diaryl, formamides, akylamides, arylamides and N-alkyl lactams; such as dimethyl formamide, dimethyl acetmamide, N-methyl,N'-Phenyl formamide, N-Methyl,N'-phenyl acetamide, N-methylpyrrolidone etc, preferably amide solvents having boiling point $>100^0$C.

According to the process of the present invention the amine solvents may be selected from aliphatic amines, cyclic amines, acyclic amines of primary, secondary and tertiary nature and aromatic amines like isoquinolines, quinolines, dialkylarylamines, pyridine and substituted pyridines. The preferred amine bases are aliphatic, cyclic or acyclic tertiary amines, pyridine and substituted pyridine bases such as lutidine. The most preferred being the pyridine and substituted pyridine bases. The substituted pyridines are symmetrical polyalkyl substituted, unsymmetrical polyalkyl sbstituted and dimethylamino pyridine like bases.

According to the process of the present invention the polyether solvents may be selected from polyethyleneglycols, diarylethers, alkylarylethers etc. The preferred being polyethyleneglycols and diaryl ethers and the most preferred being polyethyleneglycol with a molecular weight range of 200-10,000.

The solvents viz. amides, amine bases and ethers can be used as a mixture in the range of 1-99% or as neat solvents, the most preferred being as neat solvent.

According to the process of the present invention the reaction is carried out in presence of potassium iodide and the most preferred solvent pyridine.

According to the process of the present invention the reaction is carried out at a temperature between 100 - 200^{0}C for 10 - 30 hours, the preferred being 120 -160^0 C for 20-30 hours and the most preferred being 130-150^{0}C for 20 - 28 hours.

The invention is illustrated but not restricted by the description in the following examples.

EXAMPLES

COMPARATIVE EXAMPLE 1

This example illustrates the preparation of 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile according to the prior art (United States Patent No.4,136,193)

5-bromo-1—(4-fluorophenyl)-1-(3-dimethylaminopropane)- phthalane (50.0 g) and Copper (I) cyanide (13.0 g) in 36 millilitres of dimethylformamide is refluxed and worked up to obtain the crude 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base with the HPLC profile as given in Table I & II.

COMPARATIVE EXAMPLE 2

This example illustrates the preparation of 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile according to the prior art (United States Patent No.4,136,193)

5-bromo-1—(4-fluorophenyl)-1-(3-dimethylaminopropane)- phthalane (25.0 g) and Copper (I) cyanide (6.5 g) in 18 millilitres of dimethylformamide is refluxed and worked up to obtain the crude 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base with the HPLC profile as given in Table I & II.

Example 1

Potassium iodide (100g), Copper (I) cyanide (48.5g) are added to a solution of the 5-bromo-1—(4-fluorophenyl)-1-(3-dimethylaminopropane)- phthalane (100g) in pyridine (100ml). The reaction mixture is heated to 135-145^{0}C and maintained for 28 hours. The reaction mixture is cooled to 100^{0}C and poured in ammonia solution containing toluene stirred for 2 hours to get a clear separation of layers. Then the organic layer after acid base treatment is separated and washed with water twice (2x300ml) and dried with anhydrous sodium sulfate. The toluene layer is distilled to get the crude 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base 74 gm with the following HPLC profile.

Starting material 0.79%, Desmethyl impurity 0.15%, amide impurity 0.6%, higher retention time impurities <0.1% and 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile 94.4%.

Example 2

Potassium iodide (45g), Copper (I) cyanide (21g) are added to a solution of the 5-bromo-1—(4-fluorophenyl)-1-(3-dimethylaminopropane)-phthalane
(45g.) in pyridine (45ml) and PEG-400 (45ml). The reaction mixture is heated to 135-145^{0}C and maintained for 27 hours. The reaction mixture is cooled to 100^{0}C poured in to ammonia solution containing toluene and stirred for 2 hours to get a clear separation of layers. Then the organic layer after acid base treatment is separated and washed with water twice (2x100ml), dried with anhydrous sodium sulfate. The toluene layer is distilled to get the crude 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base 35.5 gm with the following HPLC profile.

Starting material 1.01%, Desmethyl impurity 0.18%, amide impurity 0.47%, higher retention time impurities <0.1% and 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile 92.3%.

Example 3

Potassium iodide (25g), Copper (I) cyanide (9.7g) are added to a solution of the 5-bromo-1—(4-fluorophenyl)-1-(3-dimethylaminopropane)-phthalane (25g) in 2,6-lutidine(25ml) and dimethylformamide (25ml). The reaction mixture is heated to 135-145^{0}C and maintained for 24 hours. The reaction mixture is cooled to 100^{0}C and poured in to ammonia solution containing toluene stirred for 2 hours to get a clear separation of layers. Then the organic layer after acid base treatment is separated and washed with water twice (2x100ml), dried with anhydrous sodium sulfate and finally the toluene layer is distilled to get the crude 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base 17.5gm with the following HPLC purofile.

Starting material 4.39%, Desmethyl impurity 0.2%, amide impurity 0.45%, higher retention time impurities <0.1% and 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile 93.0%.

Example 4

Potassium iodide (25g), Copper (I) cyanide (11.8g,) are added to a solution of the 5-bromo-1—(4-fluorophenyl)-1-(3-dimethylaminopropane)- phthalane (25g) in PEG-400 (25 ml). The reaction mixture is heated to 135-145^{0}C and maintained for 28 hours. The reaction mixture is cooled to 100^{0}C and poured in ammonia solution containing toluene stirred for 2 hours to get a clear separation of layers. Then the organic layer after acid base treatment is separated and washed with water twice (2x100ml) and dried with anhydrous sodium sulfate. The toluene layer is distilled to get the crude 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base 18 gm with the following HPLC profile.

Starting material 4.9%, Desmethyl impurity 0.54%, amide impurity 2.74%, higher retention time impurities not observed and 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile 85.1%.

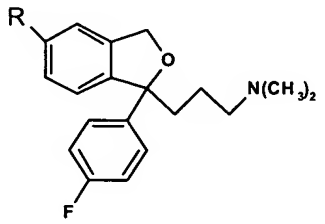
Example 5

Potassium iodide (25g), Copper (I) cyanide (11.8g) are added to a solution of the 5-bromo-1—(4-fluorophenyl)-1-(3-dimethylaminopropane)-phthalane (25g) in dimethylformamide (25ml). The reaction mixture is heated to 135-145^{0}C and maintained for 28 hours. The reaction mixture is cooled to 100^{0}C and poured in ammonia solution containing toluene and stirred for 2 hours to get a clear separation of layers. Then the organic layer after acid base treatment is separated and washed with water twice (2x100ml), dried with anhydrous sodium sulfate and finally the toluene layer is distilled to get the crude 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base 16.5gm with the following HPLC profile.

Starting material 1.91%, Desmethyl impurity 0.36%, amide impurity 8.4%, higher retention time impurities <0.1% and 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile 80.4%.

We claim:

1. A process for the preparation of crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base with substantially low levels of impurities, the process comprising reacting a compound of **Formula II**



Formula II

wherein R is Cl or Br with a cyanide source in presence of an iodide and a non polar aprotic solvent.

2. A process as claimed in claim 1 wherein the cyanide source is selected from KCN, NaCN, CuCN and $[(R')_4N]$ CN where $(R')_4$ indicates four groups which may be the same or different selected from hydrogen and straight chain or branched alkyl.

3. A process as claimed in claim 2 wherein the cyanide source is CuCN.

4. A process as claimed in claim 1 wherein the iodide is selected from the group of stable metal iodides, alkali and alkaline earth metal iodides.

5. A process as claimed in claim 4 wherein the iodide is potassium iodide.

6. A process as claimed in claim 1 wherein the solvent is selected from the group of amides, amines and polyethers.

7. A process as claimed in claim 6 wherein the solvent is pyridine.

8. A process as claimed in claim 6 wherein the solvent is lutidine.

9. A process as claimed in claim 1 wherein the reaction is carried out at a temperature between 100 – 200^{0}C for 10-30 hours.

10. A process as claimed in claim 9 wherein the reaction is carried out at a temperature between 130 – 150^{0}C for 20-28 hours.

11. A process as claimed in claims 1 to 8 substantially as herein described and illustrated by examples 1 to 5.

Dated this 4th day of January, 2002.

DILIP SHANGHVI
CHAIRMAN AND MANAGING DIRECTOR
SUN PHARMACEUTICAL INDUSTRIES LIMITED

FORM 2

THE PATENTS ACT, 1970
(39 OF 1970)

PROVISIONAL SPECIFICATION
(See section 10)

PROCESS FOR THE PREPARATION OF 1-[3-(DIMETHYLAMINO) PROPYL]-1-(4-FLUOROPHENYL)-1,3-DIHYDRO-5-ISOBENZOFURAN CARBONITRILE WITH SUBSTANTIALLY LOW LEVELS OF IMPURITIES

SUN PHARMACEUTICAL INDUSTRIES LTD.

A company incorporated under the laws of India having their office at ACME PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059. MAHARASHTRA, INDIA

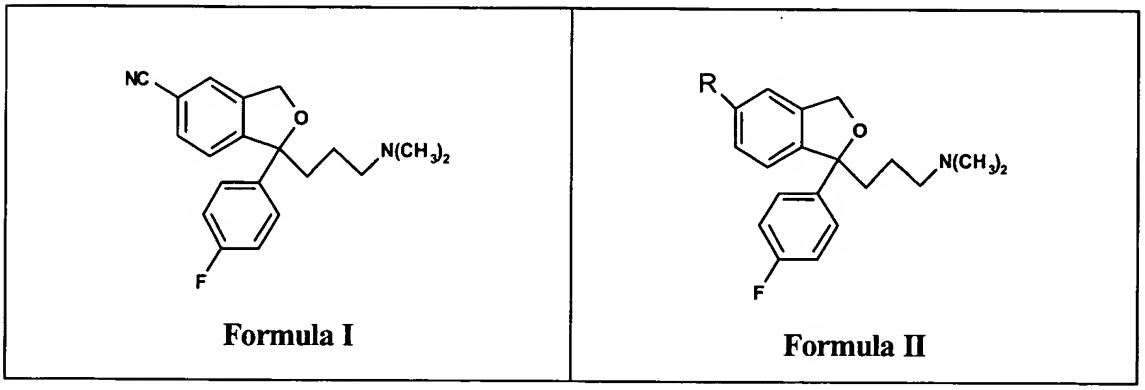
The following specification describes the nature of this invention.

PROCESS FOR THE PREPARATION OF 1-[3-(DIMETHYLAMINO) PROPYL]-1-(4-FLUOROPHENYL)-1,3-DIHYDRO-5-ISOBENZOFURAN CARBONITRILE WITH SUBSTANTIALLY LOW LEVELS OF IMPURITIES

The present invention relates to a process for the preparation of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile with substantially low levels of impurities. The compound of the process of the present invention 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile (compound of **Formula I**) commonly known as citalopram (INN Name) is a well known antidepressant.

PRIOR ART:

United States Patent No.4,136,193 (hereinafter referred to as '193) claims 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile or its pharmaceutically acceptable acid addition salt. It discloses a process for the preparation of 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile from the penultimate 5- substituted derivatives, compounds of **Formula II** wherein R is halogen or trifluoromethyl, by reaction with cyanide source.



Formula I **Formula II**

The exchange process described for the preparation of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile gives the desmethyl citalopram and other high molecular weight impurities in unacceptable amounts. Purifying such an impure material makes the process economically unviable.

PCT publication WO 0145483 claims a process for producing pure 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile from the penultimate 5- substituted derivatives, compounds of **Formula II,** wherein the R is chloro, bromo, iodo and CF_3 $-(CF_2)_n-SO_2-O-$, n-being 0,1,2,3,4,5,6,7,or 8 by reaction with cyanide source.

The above publication mentions that the exchange process described for the preparation of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile found to give the desmethyl 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile and other high molecular weight impurities in unacceptable amounts. Purifying such an impure material makes the process economically unviable.

United Kingdom Patent No. GB 2356199 discloses 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile preparation, which was made using sulfolane as a solvent, instead of dimethylformamide as reported in the '**193.** Even using sulfolane as a solvent the purity reported by HPLC is about 85%.

A very recent **United Kingdom Patent No. GB 2359811** discloses the purification method for 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile wherein the desmethyl citalopram impurity is removed by reacting with an agent which converts it into amide or an amide like neutral derivative, which subsequently can be removed by means of simple operations like acid base treatment. This patent claims use of reagents like acid halides, anhydrides, sulfonyl halides and haloformates and their derivatives to remove the desmethyl citalopram impurity by making amide or an amide like derivative, which transforms basic secondary amine i.e desmethyl citalopram to the neutral form, wherein the tertiary amine viz., the 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile remains unaltered, hence displaying the basic character, thereby making the process suitable to eliminate the non basic impurity by means of acid base treatment. However, this method does not remove the amide impurity, hence the disclosure is not a complete solution to improve the efficiency of the process.

OBJECTIVES OF THE INVENTION

The objective of the current invention is to make 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base in a substantially pure form by removal of impurities from crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base obtained using cyanide exchange process. When the cyanide exchange reaction was performed, i.e. the conversion of 5-bromo phthalane derivative to 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran, it furnished 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base with purity ranging between 75-85% by HPLC (area %). As disclosed in the patent literature we found it extremely difficult to remove the impurities and to make the desired quality of pharmaceutically acceptable product.

We observed the major impurity that is formed during the course of reaction is the amide impurity viz. 5-carboxamide –1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-phthalide, a compound of **Formula III,** along with desmethyl citalopram impurity viz., desmethyl 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile, a compound of **Formula IV**, herein after these impurities will be referred to as amide and desmethyl citalopram respectively.

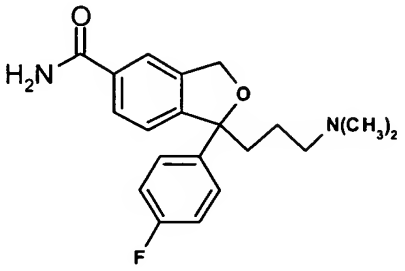
Thus for making 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile with acceptable purity, it is essential to have an efficient process to avoid the formation of impurities during the cyanide exchange process, or to eliminate the major impurities viz, the amide and desmethyl citalopram by making suitable derivatives. The objective of this invention is conversion of unwanted amide impurity to the desired product viz. to 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile along with simultaneous removal of desmethyl citalopram.

SUMMARY OF THE INVENTION

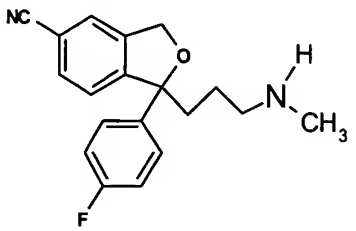
The present invention provides a process for preparing 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile with substantially low levels of impurities from crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-

isobenzofuran carbonitrile base, the process comprising reacting crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base with an amide reversal agent.

The major impurities that are formed when adopting process disclosed in the '**193** patent are compounds of **Formulae III** and **IV** and unconverted starting material. Presence of these impurities poses difficulty in purifying the crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base to the desired quality of end product.



Formula III



Formula IV

During the process the amide impurity is formed to an extent of 20%, and normally it ranges from 1 to 20% depending on the reaction conditions. The range of formation of this impurity is so wide, hence developing a process which removes the impurity in one unit operation, say crystallisation or distillation or any other purification, proved to be very difficult and unpredictable. Therefore one needs to use multiple solvent crystallisation to obtain the desired product, which makes the whole process lengthy, and also use of several reactors during purification makes it unworthy.

DETAILED DESCRIPTION OF THE INVENTION:

To devise a suitable process in order to improve purity, we envisaged that reaction of reagents, referred to herein as amide reversal agents, like oxy compounds of phosporous, acid anhydries and oxalyl chloride with the crude base would result in the coversion of 5-

carboxamide to cyanide i.e. the formation of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile back from the amide, with concomitant elimination of desmethyl citalopram by forming a neutral species like phosphorous amides.

We found upon treating crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base containing 1-20% of amide and 0.5-10% of desmethyl citalopram with the amide reversal agents of phosphorous oxy compounds, like phosphorous oxyhalides, phosphorous oxides, acid anhydrides, oxalyl chloride etc, preferably with phosphorous oxy compounds, gave substantial enrichment in purity, wherein the amide impurity reduced to below 1% due to reversal of amide to 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile and the desmethyl citalopram to below 1%. With phosphorous oxychloride the amide and desmethyl citalopram impurities reduced to below 0.5%.

The mole ratios of the amide to amide reversal agent are from 0.1 moles to 5 moles with respect to crude citalopram base; the preferred range being 0.1 to 2 mole and the most preferred range being 0.2 to 2 moles. The agents that are employed are phosphorous oxyhalides, phosphorous oxides, acid anhydrides, etc. The halides that one can use are chlorides and bromides, preferred being chlorides. The preferred agents being, phosphorous oxy halides and oxides, wherein phosphorous with valency (III, V), e.g. Phosphorous trichloride (PCl_3), Phosphorous oxychloride ($POCl_3$), phosphorous pentoxide (P_2O_5), acid anhydrides like acetic anhydride, propionic anhydride, benzoic anhydride and oxalyl chloride. The most preferred reagents being phosphorous oxychloride, and phosphorous pentoxide.

The solvents that are employed for the process are polar to non polar aprotic solvents, ethers like THF, Dioxane, etc, halogen solvents like, dichloroethane, dichloromethane, chlorobenzene, dichlorobenzene etc, hydrocarbons like hexane, cyclohexane, toluene, xylenes etc, esters like methyl acetate, ethyl acetate, benzyl acetate etc, nitriles like acetonitrile, benzonitrile etc and nitro compounds like nitromethane and nitro benzene, the

preferred being ethers, aliphatic and aromatic hydrocarbons, aliphatic and aromatic halogen solvents, esters and nitriles and the most preferred being aliphatic and aromatic hydrocarbons, ester and nitrile solvents.

The reaction can be performed at ambient to 200^0C, preferably between 50 to 200^0C, and most preferably between 50 to 150^0C. The reaction time is, between 1 to 20h, preferably between 1 to 15h, most preferably between 1 to 5h.

After the reaction completion, the reaction is discontinued by adding water. The reaction mixture thus obtained is treated with mineral acid like sulphuric or hydrochloric or other mineral acids and organic acids, to adjust the pH 1 to 4, preferably between 1 to 3 and most preferably between 2 to 3 wherein the citalopram is made to form the corresponding acid addition salt, thus making it to solubilise in aqueous medium, the non basic impurities that are formed during reaction with the reagents like phosphorous oxychloride or phosphorous pentoxide to the corresponding phosphorous amide, which can be removed by simple extraction with solvent or most of the times the solvent used for reaction itself suffices to remove the impurity.

Thus the process developed and described provides a viable method of getting high quality and better yield product by reversing the amide impurity to citalopram, and concomitant removal of desmethyl citalopram impurity by forming the neutral derivatives with the amide reversal agents. Hence this process obviates use of multiple solvents and operations making it user friendly.

EXAMPLES

Example 1

A mixture of 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-cyanophthalane(10.0g, 0.03 mol) (containing 4.7% amide and 0.72% desmethyl citalopram impurities) and phosphorous oxychloride ($POCl_3$) (2ml, 0.02 mol) in toluene (100ml) was stirred at 70^0 C under nitrogen atmosphere for 1 hour, poured into water (200ml) and adjusted the pH to 2.0-2.5 with aqueous HCl separated the toluene layer. The pH of the aqueous layer was adjusted to 9.0-9.5 with aqueous ammonia and extracted with toluene (2X100ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue checked for HPLC purity and found 0.05% and 0.23% of amide and desmethyl citalopram respectively.

Example 2

A mixture of 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-cyanophthalane(10.0g, 0.03 mol) (containing 5.85% amide and 7.43% desmethyl citalopram impurities) and phosphorous oxychloride ($POCl_3$) (2ml, 0.02 mol) in toluene (100ml) was stirred at 70^0 C under nitrogen atmosphere for 1 hour, poured into water (200ml) and adjusted the pH to 2.0-2.5 with aqueous HCl separated the toluene layer. The pH of the aqueous layer was adjusted to 9.0-9.5 with aqueous ammonia and extracted with toluene (2X100ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue checked for HPLC purity and found 0.36% and 0.45% of amide and desmethyl citalopram respectively.

Example 3 :

A mixture of crude 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-cyanophthalane(10.0g, 0.03 mol) (containing 8.27% amide and 0.33% desmethyl citalopram impurities) and phosphorous oxychloride ($POCl_3$) (2ml, 0.02 mol) in toluene (100ml) was stirred at 70^0 C under nitrogen atmosphere for 1 hour, poured into water (200ml) and adjusted the pH to 2.0-2.5 with aqueous HCl separated the toluene layer. The pH of the aqueous layer was adjusted to 9.0-9.5 with aqueous ammonia and extracted with toluene (2X100ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue checked for HPLC purity and found 0.07% and 0.12% of amide and desmethyl citalopram respectively.

Example 4:

A mixture of crude 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-cyanophthalane(5.0g, 0.01 5mol) (containing 5.8% amide and 1% desmethyl citalopram impurities) and phosphorous pentoxide (P_2O_5) (2.98g, 0.01mol) in xylene (50ml) was stirred at 140^0C under nitrogen atmosphere for 2 hours, poured into water (100ml) and NaOH flakes (5.0g, 0.125mol) was added to make reaction mixture basic, stirred for 30 minutes separated the xylene layer, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue checked for HPLC purity and found 0.49% and 0.64% of amide and desmethyl citalopram respectively.

Dated this 9th day of January, 2002.

DILIP SHANGHVI
CHAIRMAN AND MANAGING DIRECTOR
SUN PHARMACEUTICAL INDUSTRIES LIMITED

We claim:

1. A process for preparing 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile with substantially low levels of impurities from crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base, the process comprising reacting crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base with an amide reversal agent.
2. A process as claimed in claim 1 wherein the 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile with substantially low levels of impurities has less than 1% of amide impurity and less than 1% of desmethyl citalopram impurity.
3. A process as claimed in claim 1 wherein the amide reversal agent is selected from phosphorous oxyhalides, phosphorous oxides and acid anhydrides.
4. A process as claimed in claim 2 wherein the amide reversal agent is phosphorous oxy chloride.
5. A process as claimed in claim 1 wherein the molar ratio of amide to amide reversal agent is
6. A process as claimed in claim 1 wherein step (a) is carried out in an organic solvent selected from polar to non polar aprotic solvents.
7. A process as claimed in claim 4 wherein step (a) is carried out in an organic solvent selected from ethers like THF, Dioxane; halogenated solvents like dichloroethane, dichloromethane, chlorobenzene, dichlorobenzene; hydrocarbons like hexane, cyclohexane, toluene, xylenes; esters like methyl acetate, ethyl acetate, benzyl acetate; nitirles like acetonitrile, benzonitrile etc and nitro compounds like nitromethane and nitro benzene.
7. A process as claimed in claim 5 wherein step (a) is carried out in an aromatic hydrocarbon.
8. A process as claimed in claim 1 wherein step (a) is carried out at ambient to 200^0C for 1 to 20 hours.
9. A process as claimed in claim 7 wherein step (a) is carried out at 50 to 150^0C for 1 to 5 hours.
10. A process as claimed in claims 1 to 9 substantially as herein described and

illustrated by examples 1 to 4.

TABLE I : HPLC profile of reaction mass

Comp. Example	After 4 hrs				After 10 hrs				After 15 hrs				After 20 hrs			
	Product	S.M	Amide	N-des	Purity	S.M	Amide	N-des	Purity	S.M	Amide	N-des	Purity	S.M	Amide	N-des
1	77.8	10.9	0.45	0.9	73.5	2.12	0.66	6.7	71.7	2.6	0.9	4.6	67.5	2.8	2.6	1.2
2	71.7	18.0	1.48	0.59	77.7	6.8	1.7	1.4	74.8	3.9	3.1	2.4	56.4	0.5	7.1	6.3

TABLE II: High Molecular Weight Compounds (which elute at higher Retention Times)

Comp. Example	After 4 hrs				After 10 hrs				After 15 hrs				After 20 hrs			
1	RT	26.1	28.5	30.4	RT	26.1	28.4	30.4	RT	26.4	28.7	30.7	RT	26.3	28.5	30.5
	Area %	-	0.24	2.35	Area %	0.07	2.07	4.44	Area %	0.23	3.16	6.2	Area %	0.2	6.6	11.03
2	RT		30.6	33.4	RT	28.7	30.6	33.4	RT	28.8	30.7	33.5	RT	28.7	30.6	33.5
	Area %	-	0.64	0.07	Area %	0.38	3.07	0.1	Area %	0.95	4.56	0.1	Area %	3.4	13.5	-

Product 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile

S.M. Starting material i.e. 5-bromo-1—(4-fluorophenyl)-1-(3-dimethylaminopropane)- phthalane

Amide 5-carboxamide – 1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-phthalide

N-des Desmethylcitalopram